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Mechanisms of Antiarrhythmic Drug-Induced Changes in Defibrillation Threshold: Role of Potassium and Sodium Channel Conductance

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Objectives. We sought to determine which ion current predominantly affects defibrillation outcomes by using specific pharmacologic probes (lidocaine [a sodium channel blocking agent] and cesium [an outward potassium channel blocking agent]) in 26 swine.

Background. The effect of a drug on sodium or potassium channel conductance, or both, may affect defibrillation threshold values. However, it is unknown which ion channel predominates.

Methods. Each pig was randomly assigned to one of four treatment groups with two treatment phases: *group 1* = placebo (D5W) in treatment phase I followed by placebo plus cesium in treatment phase II (n = 6); *group 2* = lidocaine followed by lidocaine plus placebo (n = 7); *group 3* = lidocaine followed by lidocaine plus cesium (n = 7); *group 4* = placebo followed by placebo plus placebo (n = 6). Defibrillation threshold values and electrocardiographic measurements were obtained at baseline and at treatment phases I and II.

Results. Lidocaine increased defibrillation threshold values from baseline by 71% in group 2 ($p = 0.02$) and by 92% in group 3 ($p < 0.01$). There were no changes in defibrillation threshold values from baseline to D5W in groups 1 and 4. When D5W was added to lidocaine in group 2 and D5W in group 4, there were no significant changes in defibrillation threshold values. However, when cesium was added to lidocaine in group 3, the elevated defibrillation threshold values (mean ± SD) returned to baseline values (from 15.7 ± 3.46 to 7.55 ± 3.19 J, $p < 0.01$). Cesium added to D5W in group 1 also significantly reduced defibrillation threshold values from 7.10 ± 1.27 to 4.14 ± 1.75 J ($p < 0.01$). The effect of cesium on defibrillation threshold values was similar between groups 1 and 3, regardless of lidocaine, such that these values were reduced by 40 ± 14% and 51 ± 18%, respectively ($p = 0.28$).

Conclusions. Cesium, through potassium blockade, reverses lidocaine-induced elevation in defibrillation threshold values. The magnitude of defibrillation threshold reduction when cesium was added to lidocaine was similar to the defibrillation threshold reduction when cesium was added to placebo. Thus, inhibiting outward potassium conductance and prolonging repolarization decreases defibrillation threshold values independent of sodium channel blockade.

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Several antiarrhythmic agents have been shown to affect the defibrillation threshold of monophasic shocks (1–11). The exact mechanisms responsible for these effects are not known, although it appears that a drug's effect on sodium or potassium conductance, or both, may play a significant role (2). These studies have consistently shown (2,3,10,11) that drugs which prolong cardiac repolarization but do not affect conduction velocity (outward potassium channel blocking agents [sotalol] or sodium channel activating agents [ibutelide]) lower the defibrillation threshold. In contrast, drugs that block cardiac sodium channels and do not affect potassium conductance (i.e., lidocaine, *O*-desethyl encainide, moricizine) increase the energy required for successful defibrillation (1,2,4,5,9). Drugs that block sodium channels and also inhibit outward potassium channels have varied effects on the defibrillation threshold (i.e., quinidine, procainamide) (2,5,6,8,9). These data have led to a paradigm that indicates that drugs which block sodium channels and decrease conduction velocity without affecting the action potential duration raised defibrillation threshold values, whereas drugs that block outward potassium channels and prolong the action potential duration (in the absence of changes in conduction velocity) decrease defibrillation threshold values.

Recent evidence suggests that the effects of potassium channel blockade (evident by action potential duration prolongation) on the defibrillation threshold may predominate over the effects of sodium channel blockade (evident by a reduction in conduction velocity). Flecainide and propafenone increased defibrillation threshold values in a canine model (5,9) in which these drugs slowed conduction velocity (>20% increase in

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QRS interval) but did not change the action potential duration (<5% increase in the corrected QT interval). However, these drugs either decreased or did not affect defibrillation threshold values in a swine model (7,8) in which they slowed conduction velocity and increased the action potential duration (>40% increase in the corrected JT interval). These species-specific disparate effects on repolarization appear to be responsible for the divergent drug effects on defibrillation threshold. It is possible that a lower drug affinity for blocking canine outward potassium channels is responsible for these differences in repolarization (12). Therefore, these data imply that changes in potassium conductance influence defibrillation efficacy to a greater extent than changes in sodium conductance.

However, the blockade of the fast sodium channel remains a mechanism by which antiarrhythmic drugs increase defibrillation threshold because all antiarrhythmic drugs that have been shown (1–11) to increase defibrillation threshold values have sodium channel blocking activities. Nevertheless, it is possible that changes in outward potassium conductance can modulate the effect that a sodium channel blocking agent will have on the defibrillation threshold. Because sodium channel blockers that also block outward potassium channels have a variable effect on defibrillation threshold, it remains unknown whether the effects of reduced sodium channel activity on defibrillation threshold can be overcome by blockade of outward potassium channels.

The specific aims of the current study were 1) to determine whether blocking outward potassium conductance can reverse elevated defibrillation threshold values produced by sodium channel blockade; and 2) to determine whether the effect of potassium channel blockade on defibrillation threshold is independent of sodium channel blockade. In the present study we used pharmacologic probes with specific effects on sodium and potassium conductance to determine the interrelation between changes in ion conductance and defibrillation threshold. Lidocaine was used as a probe because it is a pure sodium channel blocker that does not affect potassium conductance and consistently elevates the defibrillation threshold (2,13). Cesium chloride was used because it is a global inhibitor of outward potassium channels (delayed and inward rectifying potassium channels), does not affect sodium conductance and has been shown to decrease defibrillation threshold values (2,14).

Methods

Animal preparation and surgical instrumentation. Domestic farm pigs weighing between 25 and 30 kg were used in this investigation. All procedures were approved by the University of Cincinnati Institution Animal Care and Use Committee before conducting the investigation. On the day before the procedure, the pigs were fasted overnight. On the morning of the investigation, the animals were premedicated with ketamine (15 mg/kg body weight) administered intramuscularly. Subsequently, pentobarbital (25 mg/kg) was administered intravenously for initial anesthesia induction. After intubation with an endotracheal cuffed tube, the animals were mechanically ventilated using a large-animal Harvard pump ventilator. A level plane of anesthesia was subsequently maintained throughout the study period using pentobarbital (demonstrated not to affect defibrillation threshold [15]), 75 to 150 mg intravenously every 30 to 60 min as needed. The femoral and external jugular veins and the femoral artery were cannulated for catheterization, drug infusion and blood collection. A combination pacing and contact monophasic action potential catheter (EP Technologies) was placed through the external jugular vein into the right ventricular apex under fluoroscopic guidance, to record monophasic action potential duration and for right ventricular pacing. A pigtail 5F Millar pressure-sensing catheter was placed through the femoral artery for blood pressure monitoring. Surface electrocardiographic (ECG) leads were placed on the four limbs for monitoring leads II and aVF. The chest was opened using a mediastinotomy. One 14-cm^2 and one 28-cm^2 titanium mesh patch electrode (models A and L 67, respectively, Cardiac Pacemakers Inc.) were sutured onto the surface of the pericardium. The large electrode was placed over the anterior and lateral wall of the right ventricle, which was perpendicular to the small electrode placed over the lateral/posterior/apical wall of the left ventricle. The electrodes were interfaced with an external defibrillator, where the right ventricular patch served as the anode. The defibrillator was capable of delivering a monophasic truncated waveform at a 65% fixed tilt with a pulse duration between 5 and 8 ms. The output of this device is determined by preset voltage adjustments (1-V increments) (Ventak ECD, Cardiac Pacemakers Inc.). The chest was closed after these procedures, and chest tubes were placed into the pleural space and drained by suction. Arterial blood gases were measured every 20 to 30 min to maintain an arterial pH between 7.37 and 7.45, partial pressure of arterial oxygen between 80 and 120 mm Hg and partial pressure of carbon dioxide between 35 and 45 mm Hg. Sodium and potassium concentrations were measured every 30 min to maintain a serum sodium concentration between 135 and 144 mEq/liter and a serum potassium concentration between 3.4 and 4.4 mEq/liter (Nova I, Baxter). Potassium concentrations remained >3.4 mEq/liter after the initial instrumentation phase of the study. Body temperature was monitored through a rectal probe and maintained at 37 to 38°C using a surgical thermal blanket. Adequate hydration was maintained using lactated Ringer solution, 2 to 5 ml/kg per h.

Study design. The experiment consisted of three phases during which defibrillation threshold and electrophysiologic variables were measured: baseline and treatment phases I and II (Fig. 1). Each pig was randomly assigned to one of four groups: *group 1* = baseline followed by placebo (D5W) followed by placebo plus cesium (n = 6); *group 2* = baseline followed by lidocaine followed by lidocaine plus placebo (n = 7); *group 3* = baseline followed by lidocaine followed by lidocaine plus cesium (n = 7); *group 4* = baseline followed by placebo followed by placebo plus placebo (n = 6). The *baseline phase* was started 30 min after completion of instrumentation. *Treatment phase I* began immediately after completion of the

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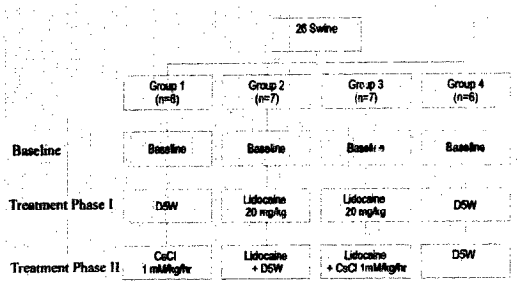

Figure 1. Study design.

baseline phase, where the treatment (D5W or lidocaine) was administered as a 10-min loading dose (20 mg/kg of lidocaine) followed by a continuous infusion (20 mg/kg per h of lidocaine) (1). D5W, which served as placebo, was given in equal volume to the lidocaine infusion. *Treatment phase II* began after the completion of treatment phase I, where lidocaine or D5W continued to be infused, and either cesium (0.25-mmol/kg load, 1-mmol/kg per h infusion) or D5W were added as a 10-min loading dose followed by a continuous infusion. D5W was given at the same infusion rate as if cesium were being infused. Defibrillation threshold and other measurements were initiated 10 min after the end of the loading dose (20 min after initiation of loading dose) for both treatment phases, so that testing began after the drug distribution phase. Blood samples were obtained every 20 min during the drug phase for analysis of lidocaine concentrations. An immunoassay method (Abbott TDx, Abbott Laboratories) was used to measure lidocaine concentrations.

Defibrillation threshold determination. Ventricular fibrillation was induced by delivering, to the right ventricle, a stimulus drive train with a 100-ms cycle length for 2 s at a stimulus amplitude of 10 V (model S8800, Grass Instruments). Defibrillation shocks were applied using the truncated exponential waveform of preset energy levels. The time between defibrillation trials was at least 4 min, but not until arterial blood pressure returned to within 10% of the preshock value. To quantitate defibrillation threshold, a previously described step-down, step-up method was used (16). Energy, impedance, pulse width and peak current delivered to the myocardium were measured by the defibrillator and subsequently priated. These values are accurate to within 10% of oscilloscopic measurements. The defibrillation threshold response for each test was modeled according to the response at each energy level within a treatment phase using an iterative computer program (MERFFIT, Cardiac Pacemakers Inc.) (16).

Electrophysiologic variables. A global assessment of ventricular conduction velocity was determined by QRS duration through surface ECG leads II and aVF during right ventricular pacing at a 350-ms cycle length. Myocardial repolarization was assessed locally by right ventricular monophasic action potential duration and globally by the JT interval through surface ECG leads during right ventricular pacing at a pacing cycle length of 350 ms. Ventricular pacing was continued for 15 s before measuring these variables. It is known that action potential duration and refractoriness take ~2 min to completely stabilize after a change in ventricular rate. However, 95% of change in these variables occurs within the first 15 beats. Our protocol measured these variables after 35 to 40 beats (15 s) and took the average of 5 consecutive beats, which tends to smooth the oscillations present after the onset of ventricular pacing.

The right ventricular effective refractory period was determined by pacing the right ventricle for 8 beats using a stimulus intensity twice the diastolic threshold at a cycle length of 350 ms followed by one premature extrastimulus. The drive train was repeated after a 2-s pause, and the extrastimulus coupling interval was decremented by 2 ms until ventricular capture failed on two consecutive attempts.

Wavelength is the spatial extent of the depolarized, and therefore refractory, myocardium occupied by an impulse. It is the distance the impulse travels during the refractory period. Thus, the wavelength of an impulse is the product of conduction velocity and refractoriness (17). The slower the conduction velocity, the less time the impulse is occupied within refractory myocardium and, thus, the shorter the wavelength. A reduction in wavelength can produce an excitable gap and allow reentry. In the present study, we approximated the wavelength by global measurements of conduction velocity and repolarization by taking the reciprocal of the QRS duration and multiplying it by the JT interval.

All electrophysiologic measurements were obtained at the start of the defibrillation threshold protocol (20 min after beginning drug infusion, i.e., postdistribution phase), 30 min after the start of the defibrillation threshold protocol and at the end of the defibrillation threshold protocol for both baseline and drug treatment phases. These values were then averaged for each study phase. Electrophysiologic measurements were made in blinded manner using a digitizing pad interfaced with a computer program (Sigma Scan, Jandel Scientific).

Data analysis. A multivariate repeated measures analysis of variance with contrast was used to test differences between groups. Within-group comparisons (measurements using the pig as its own control) were determined by using a mixed-model analysis of variance looking at the comparisons of mean values for group and treatment phases (time) with a Bonferoni correction. The percent change in defibrillation threshold values from baseline to treatment phase I and from treatment phase I to treatment phase II were correlated with changes in global measures of myocardial electrophysiologic QRS and JT intervals and impulse wavelength using regression and correlation analysis. Data are presented as mean value ± SD, and $p < 0.05$ was considered significant.

Results

Defibrillation threshold. Baseline mean defibrillation threshold values between the four groups were not significantly

Table 1. Defibrillation Threshold Values

Study Phase	ED_{50} Energy (J)	p Value	ED_{50} Peak Voltage	p Value
Group 1				
Baseline (n = 6)	6.75 ± 2.88	<0.01	306 ± 64	<0.01
D5W	7.10 ± 1.27	<0.01	298 ± 64	<0.01
D5W + CsCl	4.14 ± 1.75		240 ± 44	
Group 2				
Baseline (n = 7)	9.78 ± 3.91	<0.01	377 ± 57	<0.01
Lidocaine	15.7 ± 5.81	<0.01	464 ± 62	<0.01
Lidocaine + D5W	15.6 ± 6.60		454 ± 76	
Group 3				
Baseline (n = 7)	8.26 ± 1.80	<0.01	336 ± 34	<0.01
Lidocaine	15.7 ± 3.46	<0.01	453 ± 51	<0.01
Lidocaine + CsCl	7.55 ± 3.19		312 ± 58	
Group 4				
Baseline (n = 6)	9.02 ± 3.92		361 ± 58	
D5W	9.96 ± 4.88	NS	383 ± 77	NS
D5W + D5W	11.4 ± 4.61		408 ± 57	

Data presented are mean value ± SD. CsCl = cesium chloride; ED_{50} = median effective dose.

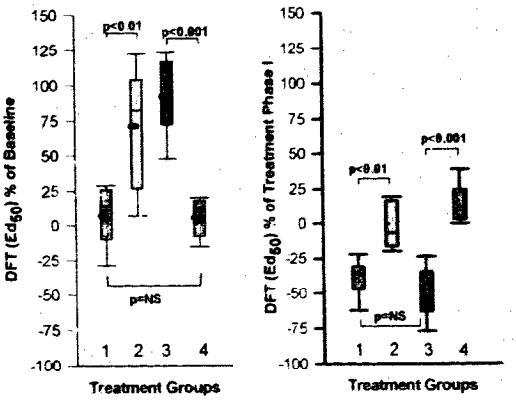

Figure 2. Box plots representing the change in median effective dose (Ed_{50}) defibrillation threshold (DFT) values from baseline to treatment phase I (**left**) and from treatment phase I to treatment phase II (**right**) for each group. In treatment phase II, cesium was added to placebo (D5W) in group 1, placebo to lidocaine in group 2, cesium to lidocaine in group 3 and placebo to placebo in group 4. **Outer edges** of boxes = 25th and 75th percentiles; **extended bars** = 10th and 90th percentiles; **bold lines** within boxes = median values; **dots** within boxes = mean values.

different (Table 1). In group 1 and 4 pigs, the defibrillation threshold values at baseline were similar to those determined during placebo treatment (Table 1). In groups 2 and 3, lidocaine significantly increased defibrillation threshold values (median effective dose) from baseline by 71% (from 9.78 ± 3.91 to 15.7 ± 5.81 J, $p = 0.02$) and 92% (from 8.26 ± 1.80 to 15.7 ± 3.46 J, $p < 0.01$), respectively. When cesium was added to lidocaine in group 3 and added to placebo in group 1, defibrillation threshold values decreased significantly by 51% (from 15.7 ± 3.46 to 7.55 ± 3.19 J, $p < 0.01$) and 40% (from 7.10 ± 1.27 to 4.14 ± 1.75 J, $p < 0.01$), respectively. In groups 2 and 4, defibrillation threshold values did not change significantly when placebo was added to either lidocaine (from 15.7 ± 5.81 to 15.6 ± 6.60 J, p = NS) or placebo (from 9.96 ± 4.88 to 11.4 ± 4.61 J).

The defibrillation threshold values in groups 2 and 3 were similar during lidocaine but were significantly different when these values were compared with those during D5W in groups 1 and 4. Overall, lidocaine increased defibrillation threshold values in groups 2 and 3 (71 ± 43% vs. 92 ± 28%, respectively), whereas D5W had no effect in groups 1 and 4 (7 ± 21% and 8 ± 14%, respectively) ($p < 0.01$) (Fig. 2). When cesium was added to lidocaine in group 3 and to placebo in group 1, defibrillation threshold values decreased significantly. Overall, cesium decreased defibrillation threshold values in groups 1 and 3 by a similar magnitude (51 ± 18% and 40 ± 14%, respectively) regardless of the presence of lidocaine ($p = 0.28$) (Fig. 2). In contrast, the addition of D5W to lidocaine in group 2 and of D5W to D5W in group 4 had no effect on defibrillation threshold values. However, defibrillation threshold values during treatment phase II in groups 1 and 3 were significantly different than those in groups 2 and 4 ($p < 0.01$) (Fig. 2).

Electrophysiologic variables (Table 2). In group 1 and 4 pigs receiving placebo in treatment phase I, no changes were seen in any of the electrophysiologic measurements. Lidocaine administration in groups 2 and 3 resulted in a significant slowing of ventricular conduction velocity, evident by a prolongation in the QRS interval during right ventricular pacing. Lidocaine also decreased the repolarization interval, evident by a reduction in the JT interval during pacing and a decrease in action potential duration. The decrease in these indexes of repolarization were of smaller magnitude than the slowing of conduction and reached significance for the paced JT interval and action potential duration at 90% repolarization in group 3 and tended toward significance in group 2. The right ventricular effective refractory period was not significantly affected by lidocaine, although there was a trend toward increased values over baseline. Lidocaine also significantly reduced the wavelength in groups 2 and 3. The addition of placebo to lidocaine in group 2 and to placebo in group 4 had no effect on electrophysiologic variables, except for a further reduction in the JT interval and a prolongation of the effective refractory period in group 2. However, the addition of cesium to lidocaine in group 3 prolonged repolarization, evident by significant increases in the JT interval and action potential duration, thereby reversing the effect of lidocaine on repolarization. The addition of cesium to lidocaine also further slowed conduction velocity, prolonged the effective refractory period and decreased heart rate. Similar findings occurred when cesium was added to placebo in group 1, but the increase in action potential duration did not reach statistical significance, and there were no changes in conduction velocity.

The percent change in defibrillation threshold values from baseline to treatment phase I showed a significant correlation

Table 2. Electrophysiologic Variables

	n	Sinus Rhythm (RR interval [ms])	Paced Rhythm 350 ms				
			QRS Interval (ms)	JT Interval (ms)	APD_{90} (ms)	ERP (ms)	Wavelength
Group 1							
Baseline	6	511 ± 93	90 ± 10	194 ± 10	235 ± 8	213 ± 14	2.2 ± 0.3
D5W	6	520 ± 75	90 ± 14	194 ± 14	231 ± 5	213 ± 14	2.2 ± 0.5
D5W + CsCl	6	583 ± 68*†	91 ± 12	206 ± 21*†	240 ± 11	222 ± 14*†	2.3 ± 0.5
Group 2							
Baseline	7	451 ± 105	89 ± 6	194 ± 20	220 ± 18	212 ± 21	22 ± 0.4
Lidocaine	7	477 ± 93	109 ± 10*	184 ± 18	213 ± 22	223 ± 19	1.7 ± 0.1*
Lidocaine + D5W	7	451 ± 65	109 ± 14*	179 ± 19*	210 ± 24	237 ± 14*	1.6 ± 0.1*
Group 3							
Baseline	7	510 ± 52	97 ± 8	200 ± 23	235 ± 10	218 ± 13	2.1 ± 0.3
Lidocaine	7	475 ± 39	116 ± 13*	179 ± 19*	220 ± 14*	223 ± 14	1.6 ± 0.2*
Lidocaine + CsCl	7	544 ± 42†	130 ± 17*†	195 ± 17†	232 ± 14†	240 ± 17	1.5 ± 0.3*
Group 4							
Baseline	6	440 ± 44	91 ± 2	182 ± 15	225 ± 16	206 ± 9.4	2.2 ± 0.3
D5W	6	442 ± 45	90 ± 2	185 ± 13	224 ± 19	207 ± 14	2.2 ± 0.4
D5W + D5W	6	447 ± 65	94 ± 5.0	189 ± 17	228 ± 14	212 ± 21	2.3 ± 0.5

*$p < 0.05$ versus baseline. †$p < 0.05$ versus previous phase. Data presented are mean value ± SD. APD_{90} = action potential duration at 90% repolarization; ERP = effective refractory period.

with percent change in QRS interval, JT interval and wavelength (Fig. 3). However the percent change in defibrillation threshold values from treatment phase I to treatment phase II correlated only with the JT interval (Fig. 3).

Lidocaine and electrolyte concentrations. The dose of lidocaine achieved steady serum concentrations from the 20-min point onward, which was the point at which the defibrillation threshold study protocol started. These concentrations ranged from 10 to 12 μg/ml in groups 2 and 3 and were not statistically different between groups when the area under the plasma concentration time curve or differences between groups over time using analysis of variance with repeated measures were compared.

Mean serum sodium concentrations did not differ among the groups during baseline and treatment phases I and II. Serum sodium concentrations ranged from 138 to 144 mmol/liter in group 1, 137 to 142 mmol/liter in group 2, 136 to 143 mmol/liter in group 3 and 136 to 145 mmol/liter in group 4 over the entire study period. Potassium concentrations remained constant in each treatment group during baseline and treatment phase I for group 1 (3.6 ± 0.1 and 4.0 ± 0.2 mmol/liter, respectively), group 2 (3.8 ± 0.3 and 4.1 ± 0.3 mmol/liter, respectively), group 3 (3.6 ± 0.2 and 3.9 ± 0.3 mmol/liter, respectively) and group 4 (3.8 ± 0.22 and 4.15 ± 0.38 mmol/liter, respectively). However, mean serum potassium concentrations during treatment phase II increased significantly when cesium was administered in groups 1 and 3 (from 4.0 ± 0.2 to 5.3 ± 0.3 mmol/liter and from 3.9 ± 0.3 to 5.0 ± 0.6 mmol/liter, respectively, $p < 0.001$), whereas potassium concentrations did not change when placebo was administered to group 2 or 4 in this treatment phase (from 4.1 ± 0.3 to 4.1 ± 0.2 mmol/liter and 4.15 ± 0.38 to 4.21 ± 0.35 mmol/liter, respectively, p = NS). The mild increase in potassium concentrations during cesium administration was similar to that reported by others (2).

Discussion

Numerous studies (1–11) have suggested that the blocking effect of a drug on sodium or potassium channels, or both, may effect defibrillation threshold values. However, these studies did not determine which ion channel predominantly affected defibrillation outcomes. There were three major findings of the present study: 1) Elevated defibrillation threshold values produced by sodium channel blockade (lidocaine) can be reversed to baseline values by blocking outward potassium conductance and prolonging repolarization through the administration of cesium chloride. 2) Potassium channel blockade (cesium) added to sodium channel blockade (lidocaine) produced an increase in repolarization time and a further reduction in conduction velocity. Despite this slowing in conduction velocity, cesium reduced defibrillation threshold values to pre-lidocaine values. 3) The cesium-induced decrease in defibrillation threshold values was independent of sodium channel blockade (lidocaine), where the magnitude of defibrillation threshold reduction when cesium was added to lidocaine was similar to the magnitude of defibrillation threshold reduction when cesium was administered during placebo. These findings support the conclusion that the effects of potassium channel blockade on defibrillation efficacy predominate over the actions of sodium channel blockade.

Previous studies. One previous study (2) investigated the relative changes in defibrillation threshold with sodium and potassium channel blockade. That study attempted to reverse the effect of lidocaine on defibrillation threshold values by using the potassium channel blocker *N*-acetylprocainamide in

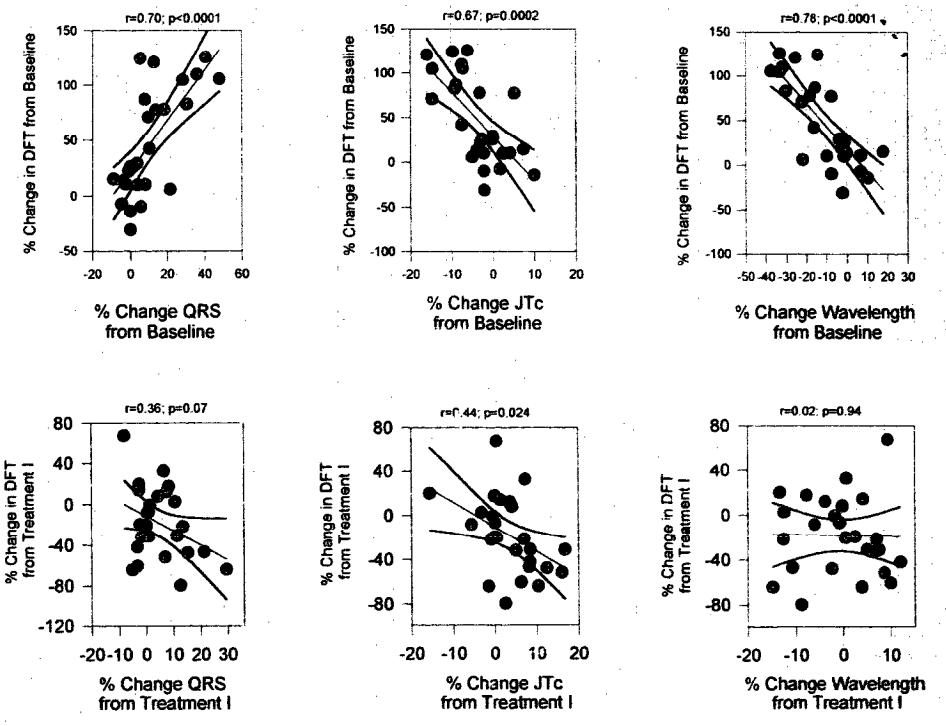

Figure 3. Relation between percent change in median effective dose defibrillation threshold (DFT) and percent change in QRS duration, corrected JT (JTc) interval and impulse wavelength from baseline to treatment phase I **(top row)** and from treatment phase I to treatment phase II **(bottom row)**.

dogs. Similar to the current study, lidocaine significantly increased defibrillation threshold values by ~100%. However, when *N*-acetylprocainamide was added to lidocaine, the defibrillation threshold values were not significantly different from those with lidocaine alone, although the defibrillation threshold values did decline by a small magnitude. Recent evidence with propafenone and flecainide (5,7–9) also suggested that the effects of potassium channel blockade on defibrillation threshold may predominate over the effects of sodium channel blockade. Although these previous studies suggest the interrelation between sodium and potassium conductance on defibrillation efficacy, they are inconclusive. The data from the current study may differ from the previous study using lidocaine and *N*-acetylprocainamide because of differences in species or the use of cesium, a more potent and less specific potassium channel blocker than *N*-acetylprocainamide. The degree of hyperkalemia caused by cesium was mild, and it is therefore unlikely that it is responsible for the differences. Nevertheless, the inferential evidence from previous studies is consistent with the findings of the present study that the effects of potassium channel blockade predominate over those of sodium channel blockade on defibrillation threshold values.

Electrocardiographic actions. In the current study, lidocaine significantly slowed ventricular conduction velocity and decreased the time to repolarization (reduction of the JT interval and action potential duration) while increasing refractoriness (postrepolarization refractoriness). These effects are consistent with previously reported data (1,2). Cesium increased the time to repolarization and the refractory period when given with placebo, which is consistent with its potassium channel blocking effects. During lidocaine, cesium had a similar effect on repolarization but also potentiated the effect of lidocaine on ventricular conduction velocity, evident by a further increase in paced QRS duration by 13%. These findings are most likely due to the effect of cesium on prolonging action potential duration. With an increase in action potential duration, the sodium channel remains in an inactivated state for a longer period of time. Because the effects of lidocaine are predominant when the sodium channel is in an open/inactivated state, the slowing of conduction velocity is greater (18,19). It is also possible that mild hyperkalemia produced by cesium could further potentiate the sodium channel blocking effects of lidocaine by depolarizing the rest membrane potential and further inactivating available sodium channels (20). Regardless of these changes in conduction velocity, the cesium-induced decrease in defibrillation threshold values was unaf-

fected. This finding substantiates the hypothesis that the effects of potassium channel blockade on defibrillation threshold values predominate over those of sodium channel blockade. Thus, the electrophysiologic mechanism by which lidocaine increased defibrillation threshold values in treatment phase I is likely to differ from the mechanism by which cesium decreased defibrillation threshold values during treatment phase II.

Our data also showed that a reduction in the JT interval and impulse wavelength and an increase in QRS duration correlated significantly with increases in defibrillation threshold values during treatment phase I. Thus, changes in several electrophysiologic variables can predict the effect of lidocaine on defibrillation threshold values. However, during treatment phase II, only the JT interval predicted the change in defibrillation threshold in the same manner as in treatment phase I. During treatment phase II, cesium in group 3 slowed conduction velocity; thus, the relation between QRS duration and defibrillation threshold was reversed. This also resulted in no net change in wavelength, and thus no correlation between wavelength and changes in defibrillation threshold. Thus, the effect of cesium on defibrillation could be predicted only by changes in the JT interval. Because there is a disparity between predictors of defibrillation between these sodium and potassium channel blockers, it is likely that these agents affect defibrillation by different mechanisms. The specific mechanism of how these agents cause changes in defibrillation outcomes cannot be determined from the present data.

Proposed mechanisms. The mechanisms by which changes in sodium or potassium conductance affect defibrillation outcomes are not understood. There are two theories of failed defibrillation: 1) The shock stimulus was not strong enough to annihilate >90% of the original fibrillation wavefronts (excitation of a critical mass); or 2) the shock stimulus annihilates the initial fibrillation wavefronts but induces a postshock electrophysiologic state that results in the generation of a new fibrillation activation front (21–23). Microelectrode recordings have shown (24,25) that the effects of high intensity shocks on depolarization (maximal diastolic potential), action potential duration and induced action potentials are not affected by tetrodotoxin (a sodium channel blocker). It is also unlikely that cesium affected the amount of myocardium excited by the shock because most agents that are pure potassium channel blockers have minimal electrophysiologic actions at fast heart rates, such as fibrillation (reverse-use dependence) (26,27). However, it was evident from the microelectrode recordings that tetrodotoxin did affect the generation of spontaneous postshock action potentials (25). Thus, it may be that sodium and potassium channel blockers do not affect the ability of the shocks to annihilate the original fibrillation front but produce postshock electrophysiologic state that can either induce or prevent the propagation of early postshock activations (reentry), resulting in failed or successful defibrillation, respectively.

Reentrant postshock activations and failed defibrillation may be caused by 1) a short impulse wavelength and thus an excitable gap; 2) unidirectional conduction block as a result of an increased refractory period dispersion; or 3) unidirectional conduction velocity slowing (anisotropic propagation) (21,28–33). It is possible that lidocaine could enhance reentry by means of all these mechanisms. Lidocaine can shorten the impulse wavelength, as we have shown, by decreasing conduction velocity while having a minimal effect on refractoriness. This would have the potential to create an excitable gap within a postshock circuit. Others (17) have shown that a reduction in impulse wavelength can predict the induction of atrial fibrillation/flutter. The other two mechanisms could also be responsible because sodium channel blockers have been shown (34–37) to increase dispersion in refractoriness and produce a greater degree of anisotropic propagation.

In contrast, cesium could prevent postshock reentry by increasing refractoriness. This action would increase impulse wavelength and thus extinguish an excitable gap. However, when cesium was given concomitantly with lidocaine, conduction velocity decreased significantly while slightly increasing refractoriness. Thus, we showed that cesium–lidocaine therapy did not affect wavelength, even though defibrillation values decreased significantly. It is also unlikely that cesium by itself can affect anisotropic conduction because this agent has no intrinsic effect on conduction velocity. It is possible that cesium could prevent reentry by decreasing refractory period dispersion because it has been shown (38) that potassium channel blockers can reduce dispersion of refractoriness during paced rhythm.

Study limitations. We used a swine model with a healthy cardiovascular system and a monophasic epicardial defibrillation system. It is unknown whether these findings can be directly extrapolated to other defibrillation systems or to diseased (infarcted or myopathic) hearts (16). Moreover, extrapolation of these findings in a swine model to humans must be done with caution. However, the results from animal studies of antiarrhythmic drugs and monophasic defibrillation have correlated with experience in humans. It has been shown (1–11,39–48) that antiarrhythmic agents that increase defibrillation threshold values in whole-animal models increase the defibrillation threshold or cause ventricular fibrillation to be refractory to defibrillation in humans with cardiovascular disease. A recent meta-analysis (46) has confirmed these observations, showing a very close correlation between animal models of defibrillation and clinical data observed in humans. Moreover, a retrospective analysis (47) indicates that antiarrhythmic agents are a responsible factor in producing high defibrillation threshold values in patients with implanted defibrillators.

Clinical implications. The clinical importance of elevated defibrillation threshold values was established when the incidence of sudden cardiac death in patients with high defibrillation threshold values (>25 J) was reported (48) to be sixfold greater than in patients with lower defibrillation threshold values (<25 J). These issues have become a daily problem because antiarrhythmic drugs have been shown (47) to affect defibrillation threshold values and are used concomitantly in 50% to 70% of patients with implanted defibrillators. We performed the present study using lidocaine concentrations

higher than those used clinically for treating ventricular tachycardia but similar to concentrations seen after bolus infusions during cardiac arrest and resuscitation (49). Data from the present study indicate that it is possible to reverse antiarrhythmic drug-induced elevation in defibrillation threshold values by antiarrhythmic drugs that prolong repolarization through potassium channel blockade. It is also possible that acute administration of a class III antiarrhythmic drug can be used as an emergency measure in patients refractory to defibrillation. This is contrary to the present advanced cardiac life support protocol, which indicates the use of lidocaine (which increases defibrillation threshold) before class III antiarrhythmic agents, such as bretylium (which decreases defibrillation threshold) (2,50,51).

Summary. The results of the present study imply that elevation of defibrillation threshold by antiarrhythmic drugs is dependent on both sodium channel activity and outward potassium conductance. However, blocking outward potassium channels lowers defibrillation threshold values independent of decreased sodium channel activity. Moreover, the present report shows that elevations in defibrillation threshold values produced by an antiarrhythmic agent can be reversed by another, which may have therapeutic potential in patients refractory to defibrillation.

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